

**Drug Metabolism and Pharmacokinetics Interest Group Report of the Interest Group Workshop
66th ASMS Conference, June 3 to June 7, 2018 San Diego, California**

Beyond Collisional Dissociation: Improving Metabolite Identification by alternative Gas-Phase Techniques

The Drug Metabolism and Pharmacokinetics (DMPK) Interest Group Workshop was held on Monday June 4 from 5:45 to 7:00 pm. Coordinator Mark Cancilla and Co-Coordinator Jonathan Josephs led the meeting by introducing the session. Approximately 80 scientists attended the workshop demonstrating interest in drug metabolism and pharmacokinetics. An expert panel shared their perspectives to spur discussion on the workshop topic. The strong attendance and active attendee participation in the discussion provide a good endorsement for continuing the DMPK-IG in future years.

A brief business meeting was held at the beginning of the workshop to review the status of the current Oral Sessions, solicit ideas for future DMPK Oral Sessions and Workshops, as well as a call for nominees and volunteers for future DMPK-IG sessions. Attendees were asked to vote for future coordinators based on a list of volunteers.

1. Review of the DMPK IG Goals

The DMPK Interest Group goals of providing a discussion forum to MS practitioners in drug metabolism, pharmacokinetics, qualitative and quantitative, non-regulated bioanalysis include sharing:

- Recent advances in techniques and methodologies for metabolite identification and pharmacokinetic bioanalysis
- Interpretation of and application of related guidance documents (i.e. MIST, ICH M3, DDI, expl. IND)
- Sharing of best practices across industry and academia
- Provide input on ASMS conference program of interest to scientists working in DMPK
- Reach out and coordinate with related groups to complement scope and broaden outreach to scientific community

2. 2018 and future DMPK IG Coordinators

2018: Mark Cancilla, Merck & Co. (Coordinator) – mark_cancilla@merck.com
Jonathan Josephs, ThermoFisher Scientific (Co-Coordinator) -
jonathan.josephs@thermofisher.com

2019: Jonathan Josephs, ThermoFisher Scientific (Coordinator)
??, Pfizer, (Co-Coordinator)

2020: ??, Pfizer, email (Coordinator)
??, ??, Co-Coordinator (TBD in 2018)

3. Update on the DMPK Interest Group's Impact on the 2018 ASMS Program

We thank the ASMS Program Vice President of Programs Richard Yost for being receptive to our requests and proposals for a comprehensive set of DMPK oriented oral sessions for the 2018 meeting. This responsiveness was reflected in the increased number of DMPK oriented Oral sessions and the positive feedback from the Interest Group attendees. The DMPK oriented oral sessions were:

- Mon AM: Imaging: Pharmaceuticals, Metabolites, and Lipids
- Mon PM: Drug Target Identification by MS

- Tues AM: Metabolomics: New Technologies and Applications
- Tues PM: Ion Mobility: Small Molecules and Clinical Analytical Challenges of Microdosing and Microsampling
- Weds AM: Quantitative Analysis in Drug Discovery and Development
- Weds PM: Microorganisms and the Microbiome
- Thurs AM: Biomarkers: Qualitative Analysis
- Thurs PM: Therapeutic Proteins, Antibodies, and Antibody/Drug Conjugates

4. Suggestions on ASMS 2018 Oral Session Topics from DMPK-IG Attendees

The attendees agreed that the current topics were still of high interest and supported expanding on them on the 2019 program, thus suggested oral session topics for ASMS 2019 are

Session Title/ Topic	Day/ Time
Ion Mobility: Small Molecules, Pharmaceuticals, and DMPK	Mon AM
Artificial Intelligence in Mass Spectrometry	Mon PM
Metabolism/Catabolism of Biotherapeutics	Tues AM
Analytical Challenges of Microdosing and Microsampling	Tues PM
Imaging: Pharmaceuticals, Metabolites and Lipids	Wed AM
Quantitative Analysis in Drug Discovery and Development	Wed PM
Antibody and Antibody-Drug-Conjugates	Thu AM
Toxicology	Thu PM

Attendees provided many additional suggestions for additional/alternate topics such as:-

Metabolism/Catabolism of Biotherapeutics
 New methodologies for enhanced small molecule fragmentation
 MS in microbiome investigations
 Artificial Intelligence in Mass Spectrometry

As an interest group we wish to continue to work with the ASMS Vice President of Programs to identify potential Oral Session topics and Oral Session Chairs. In order to support a strong DMPK focus in future ASMS meetings the DMPK IG encourages people to submit DMPK focused abstracts for oral sessions to the 2018 ASMS.

Based on feedback from Attendees and DMPK IG Members, the DMPK-IG requests returning scheduling the DMPK-IG Workshop to Monday night 5:45 to 7 pm as has been the tradition for many years in the past.

5. Discussion Topic: “*Beyond Collisional Dissociation: Improving Metabolite Identification by Alternative Gas-Phase Techniques*”

Structural elucidation of small molecule drug metabolites is often successfully accomplished by gas-phase fragmentation via collisioninduced dissociation (CID). Yet in multiple instances the site of bioactivation may not be fully resolved due to lack of informative fragments. The remaining ambiguous metabolite would then be represented by a Markush structure or with brackets placed around a particular portion of the molecule indicating the potential site or sites of bioactivation. The

ability to easily obtain more conclusive structural information of unknown metabolites by mass spectrometry-based methods continues to remain as a gap in the field. The goal of this workshop is to discuss the benefits and drawbacks of alternative gas-phase techniques that may provide additional structural information of unknown metabolites in real-world settings. Example discussions will revolve around the utility of alternative dissociation techniques that produce greater or different fragmentation pathways compared to CID, such as Electron Induced Dissociation (EID) and Ultraviolet Photon Dissociation (UVPD). Furthermore the current topics of gas-phase ion-molecule reactions and the utility of ion mobility will also be explored for their ability to facilitate the identification of unknown drug metabolites. Topics will focus on real world samples and their effectiveness on a chromatographic time scale.

An experienced panel offered comments on the current state, their experiences and provided thoughts on where the field is going. Questions from the audience resulted in a robust discussion.

Based on this background the four panel speakers provided their experiences and recommendations:

1. Isomeric Drug Metabolites Structure Elucidation by EID Mass Spectrometry– Zhidan Liang, Merck
 - Review of electron impact dissociation for generating novel small molecule fragmentation compared to CID.
 - Demonstrated clear examples of how the technique is used to provide increased structural identification confidence of unknown drug metabolites.
 - Disadvantages were noted for high-end FTICR instrumentation.
2. Leveraging Ultra-High Resolution and UVPD on an Orbitrap Platform for Structural Elucidation in Pharmaceutical Settings - Seema Sharma, Thermo Fischer Scientific
 - Charles Cheng's data from Amgen was presented
 - It was demonstrated how UVPD was able to provide increased and novel fragmentation of unknown degradants of drug product, thus quickly enhancing decisions around process chemistry.
3. Differentiation of Deprotonated Acyl, N- and O-Glucuronide Drug Metabolites by Using Tandem Mass Spectrometry Based on Gas-Phase Ion-Molecule Reactions- Edouard Niyonsaba, Purdue University
 - It was demonstrated how specific reagents are able to discern between acyl, N- and O-glucuronide drug metabolites in the gas-phase
 - The gas-phase reactions are on the msec time-scale therefore fit well with chromatographic and MS scan times
 - Disadvantage was unique and modified trap instrumentation is necessary
4. Differentiating metabolite Isomers Using Ion Mobility– Mark Cancilla, Merck
 - Demonstration of how ion mobility was able to rapidly differentiate and identify glucuronide isomers using a Waters Vion IMS system
 - CID provided no structural identifying fragments in MS/MS spectra
 - IMS was able to easily identify and assign positional isomers of two glucuronides based on their experimental collision-cross sections.

Following the brief presentations, the audience and Panel Members engaged in an extended discussion with additional viewpoints from the audience adding many points of discussion to the panel members' introduction. The audience interest in this discussion was evidenced by the fact that we had to curtail questions and comments in order for the workshop to finish.

Current Officers for the ASMS DMPK Interest Group:

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